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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,899	11/14/2005	Ronald Rodriguez	59562(71699)	9458

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,899	RODRIGUEZ ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 13-20* is/are pending in the application.

4a) Of the above claim(s) *7-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The response to election requirement dated 6/9/08 is acknowledged. Applicant's election with traverse of Group I, claim 6, is acknowledged. The traversal is on the ground(s) that a search of all claims can be made without serious burden. This is not found persuasive because it is maintained that each of the Inventions requires a separate search status and consideration. Nucleotide sequences encoding different proteins are structurally distinct chemical compounds. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequences are presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Should applicant traverse on the ground that the nucleic acids are not patentably distinct, applicant should submit evident or identify such evidence now of record showing the species to be obvious variant or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other inventions. The applicant fails to submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case, and thus these species are not obvious variants of each other based on the current record. The searches for

different groups would have certain overlap, but they are not co-extensive. M.P.E.P. states, "FOR PURPOSES OF THE INITIAL REQUIREMENT, A SERIOUS BURDEN ON THE EXAMINER MAY BE PRIMA FACIE SHOWN IF THE EXAMINER SHOWS BY APPROPRIATE EXPLANATION OF SEPARATE CLASSIFICATION, OR SEPARATE STATUS IN THE ART, OR A DIFFERENT FIELD OF SEARCH AS DEFINED IN MPEP § 808.02". Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the separate classifications. The requirement is still deemed proper and is therefore made **FINAL**.

However, as indicated previously, the claims are restricted as **linking claims**. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition

the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-20 are pending, however, claims 7-12 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-6, 13-20 are under current examination.

Specification

The abstract of the disclosure is objected to because it does not commence on a sheet separate from other materials of the disclosure. Correction is required. See MPEP § 608.01(b).

The specification contains sequence disclosures (page 48) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2) but are not present in the Sequence Listing and/or identified in the specification by sequence identifier numbers. Applicant must provide sequence identifiers, in the case that these sequences are not included in the original sequence submission, a paper copy and a computer readable copy of the Sequence Listing and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or

1.821(g) or 1.825(b) or 1.825(d). A full response to this Office Action must include a complete response to the requirement for a Sequence Listing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 17, 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating prostate cancer in a subject by intratumoral injection of a replication conditional adenovirus vector comprising a prostate-specific TRE operably linked to a nucleotide sequence encoding an E1A/AR chimeric protein, does not reasonably provide enablement for treating prostate cancer in a subject by administering said vector from a site remote from the tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most

relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

In the specification, the applicant contemplates administering the recited vector by any route of administration to a subject in need. In a post-filing publication, the applicant's group illustrated a single intratumoral injection of adenovirus vector expressing E1A-AR chimera was able to significantly block tumor growth in a prostate cancer xenograft model mouse (e.g. figure 6). However, neither the specification nor the post-filing publication establishes that administering said vector from a site remote from the cancer would achieve a tumor suppression effect.

Turning to the state of the art, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired cells *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ABILITY TO TARGET A GENE TO A SIGNIFICANT POPULATION OF CELLS AND EXPRESS IT AT ADEQUATE LEVELS FOR A LONG ENOUGH PERIOD OF TIME" (page 53, first paragraph). *Deonarain* reference gives high hope to targeted gene delivery, but the discussed strategies are still under investigation, and at the time, they were much less efficient than viral gene delivery (Conclusion), *Deonarain* teaches, "GENE DELIVERY REMAINS THE MAJOR TECHNOLOGICAL STUMBLING BLOCK IN GENE

THERAPY STRATEGIES", (2nd paragraph, page 54). The state of the art teaches that the vector and the route of administration are critical for cancer gene therapy, and systemic administration has yet to become practical. For example, *Vile et al* (Gene Ther 2000;7:2-8) teach, "SO FAR, THERE HAS BEEN A DISAPPOINTING INABILITY TO REACH TARGET CELLS WITH SUFFICIENT EFFICACY TO GENERATE HIGH ENOUGH LEVELS OF DIRECT KILLING" (abstract), "IN TRUTH, NO SUCH SYSTEMICALLY TARGETED VECTORS EXIST YET" (paragraph bridging columns 1 & 2, page 4). Adenovirus is the preferred embodiment of instantly claimed invention, however, at a post-filing date, *Green et al* (Cancer Gene Ther 2002;9:1036-42) teach, "THE DEVELOPMENT OF A TARGETED ADENOVIRAL VECTOR, WHICH CAN BE DELIVERED SYSTEMICALLY, IS ONE OF THE MAJOR CHALLENGES FACING CANCER GENE THERAPY" (e.g. abstract), the difficulties are due to multiple factors such as pre-existing antibodies, and cellular tropism. Even for the promising ONYX virus, there are several hurdles need to be overcome before achieving an effective tumor-specific systemic therapy. In view of such, the specification fails to support the full scope of the claims.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to

> be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Rodriguez et al* (Cancer Res 1987;57:2559-63), in view of *Suzuki et al* (Cancer Res 2001;61:1276-9) and *Becker et al* (Mole Cell Biol 1989;9:3878-87).

The claims are drawn to a composition comprising a prostate-specific replication conditional adenovirus vector comprising a prostate-specific transcriptional regulatory element (promoter+enhancer) operably linked to a nucleotide sequence encoding a chimeric protein fused between an adenoviral E1A and the Androgen Receptor (AR) or fragment thereof, and the methods of making and using such for treatment of prostate cancer.

Rodriguez teaches a prostate-specific conditional replication-competent adenoviral vector comprising a prostate-specific promoter driven the expression of E1A, and a method of using such to selectively suppress prostate cancer cell growth (see e.g. the abstract and figures). *Rodriguez* teaches when including an androgen responsive element fused to the prostate-specific minimal enhancer/promoter unit (figure 1), prostate selectivity of the virus was enhanced

(e.g. column 1, page 2559, table I and figures 3A-B); and in the presence of androgen, the PSE activity is induced and the virus titer increased 5 to 7-fold (e.g. column 1, page 2561). The teaching of *Rodriguez* establishes it was well known in the art a prostate-specific conditional replication adenovirus comprising a prostate-specific transcriptional regulatory element expressing E1A was able to specifically suppress prostate cancer cell growth, and androgen would enhance such cancer inhibitory effect. *Rodriguez* does not teach fusing E1A with an androgen receptor.

Suzuki supplemented the deficiency by establishing it was well known in the art that including a partial androgen receptor gene in a PSA gene construct enhances PSA promoter activity. *Suzuki* teaches the transcription of the PSA gene is strictly androgen dependent, and its promoter activity is very weak at low concentrations of testosterone as is the case of prostate cancer patients (e.g. the abstract). *Suzuki* inserts the partial AR gene in the PSA gene construct including the PSA promoter, which enhanced PSA promoter-driven transgene expression (e.g. Figures 1A-1B).

Becker supplemented *Rodriguez* in view of *Suzuki* by establishing it was well known in the art that fusion of adenovirus E1A to a hormone receptor created a hormonally inducible viral transactivator.

Apparently, it was well-known in the art that including the androgen receptor gene in a construct enhances the transcriptional activity of PSA promoter, and E1A may serve as a hormone inducible viral transactivator when fused with a hormone receptor. Accordingly, it would have reasonably suggested

to the skilled in the pertinent art to fuse the E1A with AR in the construct taught by *Rodriguez* to create an androgen hormonal inducible E1A expression construct as suggested by *Becker*, with a reasonable expectation of success. The ordinary skilled in the art would have been motivated to do so because androgen enhances PSA promoter activity as taught by *Suzuki,* and androgen increases the titer and specificity of the prostate replication conditional adenovirus as taught by *Rodriguez*.

As to the claimed SEQ ID No: 1, it is the fusion sequence between AR and E1A. Since both sequences were separately known in the art, it was within the level of the skilled in the art to make the fusion sequences according to the known sequences as suggested by the combined teachings.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7:30 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
July 18, 2008